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# Safety and efficacy of non-surgical treatments for chronic post-radiation cystitis: a systematic review

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**Introduction** Post-radiation cystitis is a complication of external beam radiation therapy, for the radical treatment of pelvic malignancies as radical treatment for pelvic malignancies. Chronic, refractory, post-radiation cystitis is problematic in its management, mainly when a conservative approach is preferred. Conservative methods are the first line of treatment, especially since the area has been irradiated, making surgical treatment more challenging.

The objective of this systematic review is to evaluate the effectiveness and safety of conservative methods for the management of post-radiation cystitis. All non-invasive methods were included in the research, in patients over 18 years of age undergoing pelvic radiation therapy.

**Material and methods** We conducted a systematic search for comparable studies on the conservative treatment of chronic post-radiation cystitis, analysing the efficacy and safety of these techniques, based on a specific protocol. The PubMed, Scopus, and CENTRAL databases and the grey literature were searched. Risk control of the individual papers was carried out using the RoB2 and ROBINS-I tools.

**Results** A total of 282 papers were reviewed, of which 6 were included in the review: 3 randomised clinical trials and 3 non-randomised studies. Each of these studies investigated a different treatment, using a different population as control group, so it was not possible to conduct a meta-analysis of the studies.

**Conclusions** Although most conservative measures appear to be successful in the management of post-radiation cystitis, more studies, especially randomised clinical trials, are needed before an algorithm of conservative methods can be created.

Key Words: radiation cysticis ‹› pelvic malignancies ‹› formalin ‹› silver nitrate

## INTRODUCTION

Pelvic irradiation is considered a valid therapeutic option for the treatment of pelvic malignancies, either as primary treatment, adjuvant to surgical treatment, or in cases of local disease recurrence [1]. A large proportion of cancer survivors suffer from side effects of radiotherapy because irradiation of the pelvic organs carries the risk of radiation damage to surrounding healthy organs, a pathology called pelvic radiation disease (PRD), and in particular post-radiation cystitis if it affects the urinary bladder.

The bladder epithelium is more susceptible to radiation damage, probably due to the reduced rate of cell proliferation. Urine is a particularly strong irritant, and as a result, when it comes into contact with the deeper layers of the bladder, it causes irritation and inflammation of the bladder wall. Bladder irradiation may cause destructive endarteritis, i.e. damage to small arteries due to swelling of its inner lining, and consequently, due to reduced

tissue perfusion, ischaemia that leads to atrophy and fibrosis, resulting in haematuria. Fibrosis, if extensive, can lead to decreased bladder capacity, frequency, urgency, and even incontinence; this can be functional incontinence due to intrinsic sphincter deficiency or urge incontinence due to reduced bladder capacity and reduced bladder compliance/detrusor overactivity [2].

Chronic post-radiation cystitis develops over a period of 6 months to 20 years after radiotherapy [3] with varying degrees of haematuria and/or severe lower urinary tract symptoms (frequency, dysuria, and urgency).

## Treatment options for chronic post-radiation cystitis

Conservative management is usually the first line of treatment and includes hydration and diuresis, bladder catheterisation, clot evacuation, and continuous or intermittent bladder irrigation. If haematuria persists, bladder irrigation or instillations with a variety of substances have been described including aluminium salts (alum), silver nitrate, formalin, and hyaluronic acid with/without chondroitin, each with varying degrees of efficacy and bladder toxicity.

**Aluminium salts** (aluminium ammonium sulphate or aluminium potassium sulphate) have been used for the treatment of haemorrhagic cystitis since the 1980s [8]. The mechanism of action is via vasoconstriction and reduction of the permeability of the bladder capillaries [9]. There have been rare reports of absorption and concomitant nephrotoxicity caused by aluminium salts in patients with normal renal function, as these salts are excreted through the kidneys [9–11]. According to Westerman et al., about two-thirds of patients experienced remission of post-radiation cystitis symptoms, and one-third of those maintained these results, suggesting its efficacy as first-line treatment [12].

**Formalin**, an aqueous solution of formaldehyde, was first introduced in 1969 as a therapeutic option for recurrent haemorrhagic cystitis [13]. Formalin causes occlusion of bladder capillaries and stabilisation of urothelial proteins [14, 15]. Several adverse effects have been reported, such as hydroureteronephrosis due to urinary reflux and even renal failure, reduced bladder capacity, and urinary fistulas, depending on the concentration of instilled formalin [16–18].

**Silver nitrate** is a cauterising agent. When silver nitrate is mixed with water nitric acid is produced, which has cauterising properties [19]. Since most relevant studies were carried out in children with haemorrhagic cystitis caused by cyclophosphamide, silver nitrate plays a limited role in the management of adults with haemorrhagic cystitis [20–22].

**Hyaluronic acid** seems to effectively restore the protective layer of glycosaminoglycans (GAG) in the bladder urothelium. The protective coating of the bladder urothelium together with the narrow interstitial connections create the main barrier between the bloodstream and the urine. This barrier, which is destroyed by radiation, is restored to a certain extent with hyaluronic acid [6].

Systemic conservative treatments include **hyperbaric oxygen therapy**, WF10, and pentosan polysulphate. Hyperbaric oxygen therapy is administered in specific compression chambers, which provide 100% $O_2$ at a designated pressure (about 2 atmospheres) for a specific period of time (usually 90 minutes, with intervals of atmospheric air inhalation). The aim is to reverse hypoxia in the bladder tissue, which is achieved through better diffusion of oxygen into the tissues promoting neoangiogenesis formation. The disadvantages of this treatment include claustrophobia, limited availability [7], and adverse effects related to the increased pressure, such as rupture of the eardrum and dizziness. Literature indicates that this method has an efficacy of 60–92% [23], with patients with less severe symptoms showing a better and more durable response.

**WF10**, an intravenous derivative of TCDO (tetrachlorodecaoxide), is a molecule that acts by modifying the immune response. Once the bladder inflammation has stopped after irradiation, healing of the bladder urothelium begins, resulting in the shutting and healing of the capillaries that cause haemorrhagic cystitis. This results in remission of haematuria but also of urinary urgency [24–26]. The first trial by Srisupundit et al., in a series of 20 patients, showed a remission in symptoms of up to 80% with no significant side effects. This was followed by 2 major studies by Veerasarn et al., in 2004 and 2006, in which WF10 was compared to a control group receiving bladder irrigations and transfusions, also in combination with conventional therapy without a control group, with very good results (14/16 showed complete remission of symptoms, with mild adverse effects) [28].

**Pentosan polysulphate** is a semi-synthetic molecule that functions as a synthetic GAG. GAG coat the bladder epithelium internally, so this semisynthetic glycosaminoglycan replaces the damaged GAG layer. Case reports of oral pentosan polysulphate showed an improvement in haematuria, which persisted after the initial administration and dose reduction to maintenance levels, with no adverse effects [4, 5].

## MATERIAL AND METHODS

### Study characteristics

This is a systematic review of the literature from the first recorded report on chronic post-radiation cystitis up to December 2023, aimed at finding all papers that meet the inclusion criteria.

### Inclusion and exclusion criteria

For a study to be included in this systematic review it had to involve adult patients with symptoms of chronic post-radiation cystitis, presence of symptoms for 6 months after the end of radiotherapy, or persistence of symptoms for more than 6 months. Patients participating in the study should have undergone radiotherapy for the treatment of pelvic malignancies.
For a study to be excluded from this protocol, haematuria must be associated with a cause other than post-radiation cystitis. Studies that focused on haemorrhagic cystitis resulting from chemotherapy were also excluded.

### Study protocol

This systematic review looked for comparative randomised clinical trials and non-randomised retrospective and prospective clinical trials. Articles written in English, German, French, and Spanish were accepted. Single-arm trials, either randomised clinical trials or non-randomised interventional studies (non-comparative studies), were excluded.
The searched databases were PubMed/MEDLINE, Scopus, LILACS, and Cochrane/CENTRAL. The last search was performed on 30/12/2023. A screening of literature references relevant to this study was carried out to identify and include them during the initial selection of papers using the "snowball" method and screening of the references of these papers. Further research using common search engines was carried out in order to find "grey" literature references related to this topic (Google Scholar, theses or dissertations).
The PubMed/MEDLINE search sequence was developed as follows: ("Radiotherapy" OR "Radiation injuries" OR "radiotherapy") AND ("Urination disorders" OR "Haematuria" OR "Fistula" OR "Urinary Frequency" OR "Urinary Frequency" OR "Urinary Urgency" OR "Urinary Incontinence" OR "Bladder Fibrosis" OR "Urinary Stricture" OR "Urethritis" OR "Bladder Neck Obstruction" OR "Ureteral Obstruction" OR "Hydronephrosis" OR "Cystitis" OR "Telangiectasis"). The above search sequence was modified accordingly to search the other databases. The full search sequence can be found in the appendix.

### Technical characteristics

Two authors (ND and EZ) executed the paper search algorithm. After removing duplicate work, the titles and abstracts of the remaining papers were reviewed. Papers whose full text was not available, or the full text was in a language other than the above-mentioned accepted languages, were excluded from the study. The selection process was done according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1).
Data extraction was carried out by 2 researchers (ND and EZ). In this systematic review, both randomised and non-randomised clinical trials were included. For randomised clinical trials, the RoB2 tool was used. The control fields of this tool include the following: selection error, execution error, intervention finding/identification error, decay error (incomplete result data), reporting error, and various other types of error (Figures 2, 3).
For non-randomised studies, the ROBINS-I (risk of bias in non-randomised studies of intervention) tool was used, which checks 7 areas of bias, categorising each study as low, moderate, high, and unclear risk. These areas of error include the following: confounding, selection, classification in the intervention, deviation from the therapeutic intervention, and missing data in the measurement of outcomes and in the selection of reported outcomes error (Figures 4, 5).

### Objectives of the study

The main objective of this systematic review is to identify all studies on various non-surgical interventions for the treatment of chronic post-radiation haemorrhagic cystitis, and if possible to compare the results of these studies so that a conclusion can be drawn about the efficacy and safety of the individual methods. This review will attempt to find all the relevant studies of interventions for the treatment of chronic post-radiation cystitis, provide a quantitative comparison and if possible, propose a treatment algorithm.

## RESULTS

### Search results

The search retrieved 1334 studies from PubMed/MEDLINE, 3,252 from Scopus, 15 from LILACS, and 241 from Cochrane/CENTRAL, for a total of 4,842 papers. Eight papers were retrieved from the ClinicalTrial.gov database, but it was not pos-

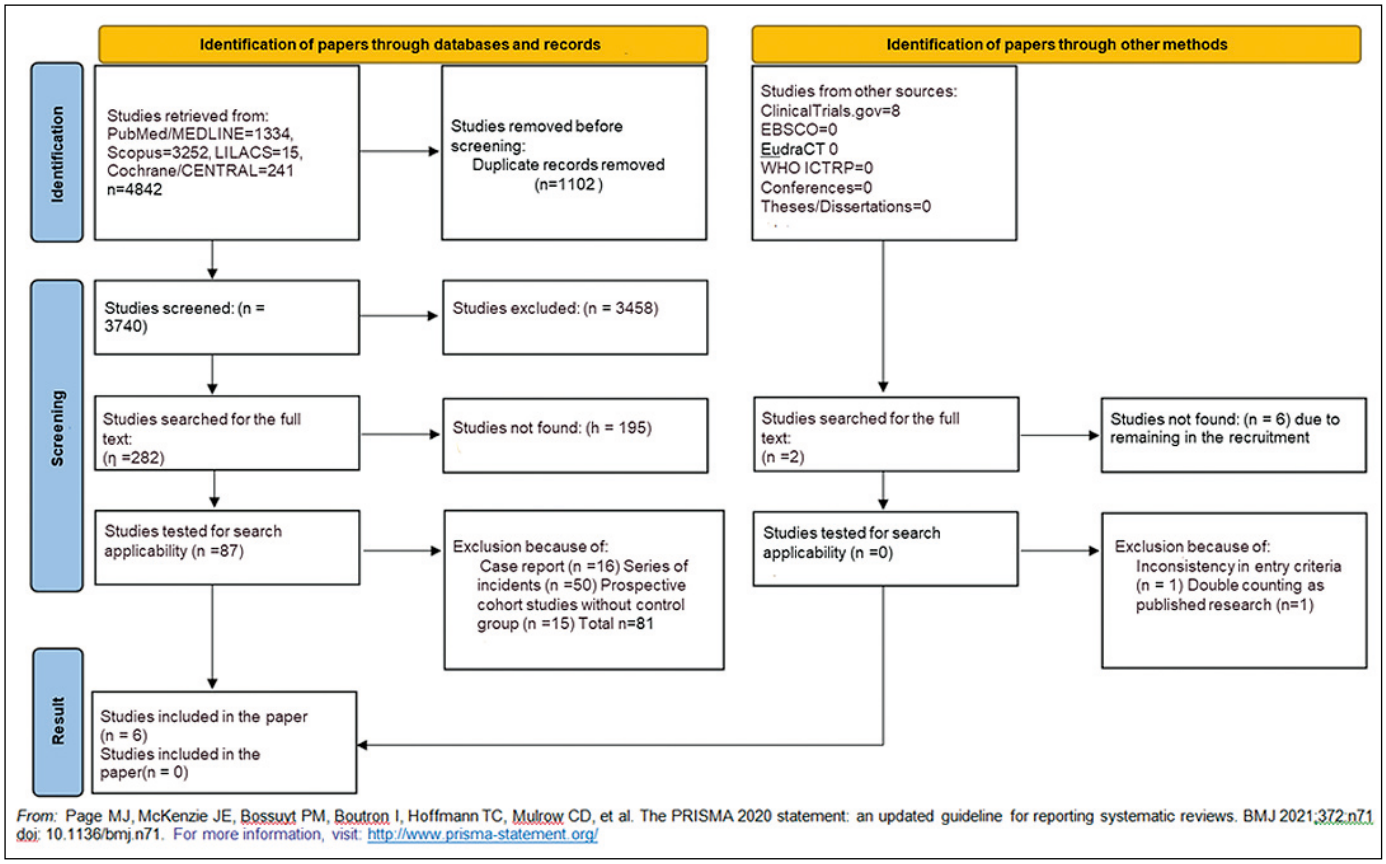


**Figure 1.** *Papers selection process PRISMA flow diagram.*

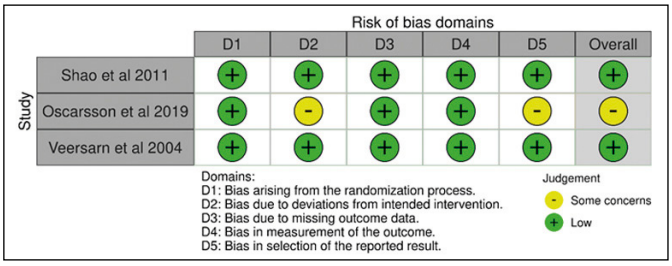


**Figure 2.** *Error risk graph, using the ROB2 toll.*

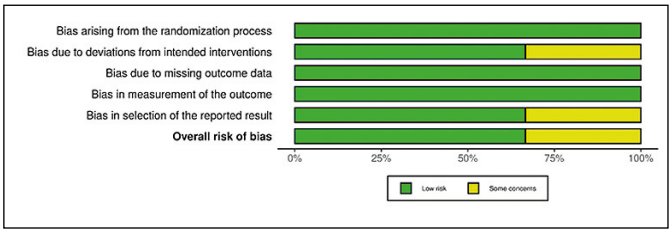


**Figure 3.** *Total risk of error by category, using the ROB2 toll.*

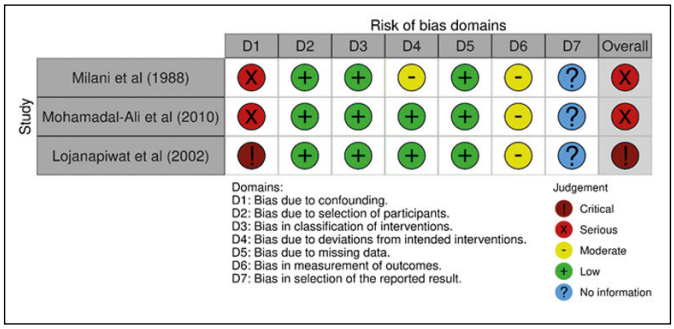


**Figure 4.** *Error risk graph, using the ROBINS-I toll.*

sible to find papers related to the topic in the EudraCT, WHO ICTRP, EBSCO databases, conference proceedings that were not already published, and theses and dissertations. Of the total 4,850 papers, after performing duplicate removal using the Mendeley software, 3,740 studies were title-screened. Of these papers, 3,458 were considered irrelevant to the study's entry criteria, leaving 282 papers to search for full text. Of these papers, the full text was available for 87.

In total, 81 papers were excluded from further statistical synthesis and analysis. Sixteen of those were case reports, while 50 were simple case studies. Finally, the 15 papers excluded were prospective cohort studies but did not include a control group. In conclusion, 6 papers remain to be studied,

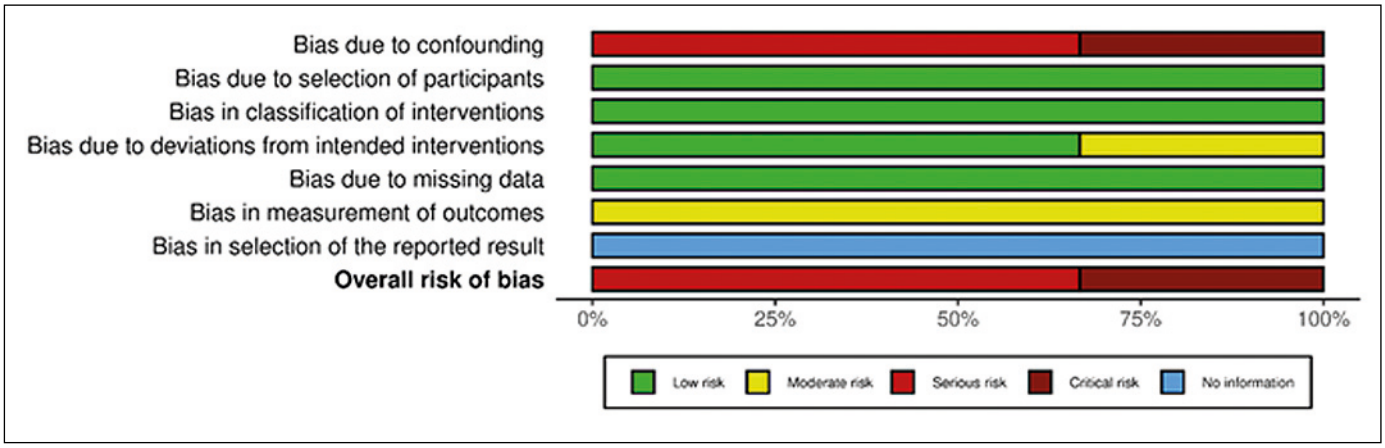


**Figure 5.** *Total risk of error by category, using the ROBINS-I toll.*

of which 3 were randomised clinical trials, and 3 were prospective or retrospective studies using 2 groups, either a control group or a second group receiving an intervention.

## Characteristics of the included studies

Of all the eligible studies, the three randomised clinical trials used different interventions for treating chronic post-radiation cystitis, namely hyperbaric oxygen, WF10, and hyaluronic acid compared to hyperbaric oxygen. More specifically, Shao et al. studied the effect of intravesical instillation of hyaluronic acid on post-radiation cystitis and the use of hyperbaric oxygen, as well as a comparison of these 2 methods, in a cohort of 36 patients with haemorrhagic cystitis [27]. Symptoms of haematuria, frequent urination, and pelvic pain (on a scale of 0–10) were studied to evaluate the effect of the 2 therapeutic methods. Response to treatment was defined as the day of absence of symptoms (haematuria and frequent urination). Partial response was considered the presence of macroscopic haematuria and absence of blood clots. All other results were considered as no response to treatment. There was no statistically significant difference in the improvement of patients in the 2 groups. In terms of urinary frequency, there was a significant improvement with treatment in both groups at 6 months, but this improvement was only significant in the hyaluronate group at 12 months after treatment. The main adverse effect of hyaluronic acid was urinary tract infection due to catheterisation, with an increased incidence compared to the hyperbaric oxygen group at 6 months, but no statistically significant difference at 12 and 18 months.

The study by Veerasarn et al. compared the effect of the WF10 agent in combination with standard clinical therapy on post-radiation haemorrhagic cystitis with that of standard clinical treatment alone, i.e. the use of saline solutions for bladder irrigation combined with removal of the clots, administration of iron supplements, antispasmodics, and antibiotics, and transfusion if deemed necessary [28]. The patients in both groups were women after irradiation of the primary lesion at least 6 months before the onset of symptoms of post-radiation cystitis. Haematuria was classified using the LENT-SOMA criterion. Patients were followed up at 12, 24, 36, and 52 weeks after the end of treatment, or at a different time if the patients disease relapsed. From the treatment group 37 of 50 patients showed complete remission of haematuria, compared to 32 of 50 patients in the control group, with no statistically significant difference between these 2 groups ($p = 0.28$). Of the group of patients who initially responded to treatment, 17 of 37 presented with recurrence of haematuria, compared to 24 of 32 of the control group, a difference that is statistically significant ($p = 0.01$).

Oscarsson et al. studied the effect of hyperbaric oxygen on chronic post-radiation cystitis in 87 patients from 5 Norwegian hospitals, using the EPIC (Expanded Prostate Index Composition Score) system as the measurement scale, and in particular the specialised section for the urinary system [29]. Patients were randomised in 2 groups: a group of intervention with hyperbaric oxygen comprised of 30–40 sessions at 240–250 kPa for 80–90 min with 100% $O_2$, and a control group, where the usual treatment was applied. The difference between these 2 groups in terms of mean patient scores on the EPIC system before and after the intervention was an improvement of 10.1 in the hyperbaric oxygen group and 7.7 in the control group. Regarding the adverse effects of the intervention, they occurred in 17 of 41 patients, and most were first- or second-degree (barotrauma, myopia from oxygen administration)

complications that are self-limiting or easily managed without the need to discontinue treatment.

The 3 non-randomised clinical trials also studied the administration of different treatments for post-radiation cystitis, namely the administration of flavoxate hydrochloride in various doses without the use of a control group, intravesical administration of formalin, either through instillation or by applying patches, placental extract instillation, and the use of hyperbaric oxygen. There was also a difference in the symptom being treated in each of these studies. More specifically, Milani et al. studied the urgency after radiotherapy and how it is treated with different concentrations of flavoxate hydrochloride [30]. A sample of 34 women with symptoms of urgency after pelvic irradiation were treated with flavoxate hydrochloride in 2 different intervention groups, with daily doses of 600 mg and 1,200 mg, respectively. There was an improvement in the overall clinical condition of patients in the 600 mg group (9/21 or 43%) and in the 1,200 mg group (8/13 or 61%), a statistically non-significant difference. The urodynamic monitoring of these patients showed an improvement in total bladder capacity, first urge to urinate, and pressure at maximum capacity (the 1,200 mg group prevailed in terms of improvement, marking a statistically significant difference compared to the 600 mg group).

The remaining papers analysed the effect of each active substance on haematuria. The study conducted by Lojanapiwat et al. investigated the effect of formalin on persistent haematuria caused by post-radiation cystitis [31]. Patients participating in this study (n = 19) were divided into 2 groups, one group receiving 4% formalin intravenously (n = 11) and the second receiving 10% formalin through application of impregnated gauzes (n = 8). In the first 24 hours after treatment, patients' urine was clear in 9/11 (82%) and 6/8 (75%) patients in the 2 groups, respectively. Four adverse effects occurred in the first group of patients, namely bilateral hydronephrosis with anuria (n = 2), vesicovaginal fistula (n = 1), and death due to sepsis (n = 1). No adverse effects occurred in the second group of patients.

Mohamadal-Ali et al. studied the effect of hyperbaric oxygen in relation to conservative treatment for haematuria in patients with post-radiation cystitis [32]. Patients were divided into 2 groups, with the first group (n = 10) receiving hyperbaric oxygen treatment and the second group (n = 4) receiving conservative treatment only. In the results, 2 of 10 (20%) and 2 of 4 (50%) patients in both groups had symptom remission. Hyperbaric oxygen treatment was well tolerated without any adverse effects (Table 1).

## DISCUSSION

The studies that were included in this review are different in design; 3 were randomised clinical trials and 3 were non-randomised studies, with varying degrees of risk of error. Moreover, each of the studies investigated a specific symptom. The study by Shao et al. [27] focuses on the comparison of two methods, hyaluronic acid and hyperbaric oxygen, for the treatment of post-radiation cystitis. In the study by Veerasarn et al. [28] systemic administration of WF10 was used as a therapeutic method, while in the study by Oscarsson et al. [29] hyperbaric oxygen was administered to treat the symptomatology of post-radiation cystitis.

In the non-randomised studies, i.e. the studies by Milani et al. [30] and Lojanapiwat et al. [31], focus was placed on comparing a treatment applied in a different way, in the first study by doubling the dose of the administered medicine, and in the second by modifying the way the therapeutic substance is introduced inside the bladder. The study by Mohamadal-Ali et al. [32] tested the efficacy of hyperbaric oxygen for the treatment of post-radiation cystitis. Taking all the above into account, it was considered that a meta-analysis of these studies cannot be performed because there is a risk of increasing the error in non-randomised clinical trials.

Several papers referred to the creation of an algorithm to have a more methodical approach to the conservative treatment of this condition. For example, the study by Vanneste et al. [33] analysed all possible treatment approaches in patients with acute and chronic cystitis and urethritis of post-radiation aetiology. In this paper, categorisation was based on symptoms: the first category defines haematuria (haemorrhagic post-radiation cystitis) as its predominant symptom, while the second defines inflammation (symptoms of urgency, dysuria, and frequent urination) as its predominant symptom. The first case was treated with all the preparations and methods mentioned above in this paper (briefly: oral preparations, intravesical instillation or irrigation, embolisation of vessels, or cauterisation of the bladder mucosa). In the second case, anticholinergic, corticosteroid, non-steroidal anti-inflammatory medicines, and $\alpha 1$ and $\beta 3$ adrenoreceptor antagonists were used (Figure 6).

A different treatment algorithm is presented by Alesawi et al. [34], who try to treat only haematuria in patients with post-radiation cystitis This algorithm includes the use of hyperbaric oxygen, but as a last line of conservative treatment, before the application of interventional methods (Figure 7).

A noteworthy point of reference is the study conducted by Ju et al. [35], in which an attempt was made to treat chronic post-radiation cystitis (to treat haematuria) using 5 consecutive steps in 6 cancer centres in China, through a retrospective study of 650 patients with moderate and severe haematuria. While until recently there was a simple synthesis of methods and proposal of the authors, here an attempt was made to study the effectiveness of a combined method.

The first line of treatment included administration of antibiotics, analgesics, and epsilon-aminocaproic acid, as well as other haemostatic agents to treat haematuria. If there was no partial or complete remission of symptoms, in the second line of treatment patients underwent intravesical instillations of thrombin or hyaluronic acid solutions. Patients with partial and no remission of haematuria were managed with endoscopic cauterisation of the mucosa and clot evacuation. One week after the application of this treatment, if haematuria persisted, patients were managed with the fourth line of treatment, i.e. selective embolisation of the intrapelvic branches of the internal iliac arteries bilaterally. In the fifth line of treatment, patients who did not show complete remission of their symptoms were treated with 100% hyperbaric oxygen at 2.36 atmospheres for approximately 90 minutes, for a total of 40 sessions.

This study clearly demonstrates that the combination of invasive and non-invasive methods with a sequential application of increasing levels of intervention seems to have better results, especially in the most severe cases, as well as better patient compliance to treatment.

**Table 1.** *Type of treatment cystitis – results, adverse effects*

| Paper | Gender | Age | Cystitis grade | Type of treatment | Results | Adverse effects |
|---|---|---|---|---|---|---|
| Shao et al. (2011) [27] | Hyaluronic acid: 6 women, 10 men Hyperbaric oxygen: 8 women, 12 men | Hyaluronic acid: 59.3 (46–74) Hyperbaric Oxygen: 60.3 (44–78) | Hyaluronic acid: I = 0, II = 6, III = 10, IV = 0 Hyperbaric oxygen: I = 0, II = 10, III = 10, IV = 0 | Hyperbaric oxygen 2.5 atmospheres (n = 20) Hyaluronic acid instillations (n = 16) | Full remission: hyperbaric = 9 hyaluronate = 8 Partial remission: hyperbaric = 6 hyaluronate = 4 | Not mentioned |
| Veerasarn et al. (2004) [28] | WF10:51 Women Control group: 51 women | WF10: 51 (26-70) Control group: 52 (28–70) | WF10: : I = 0, II = 43, III = 8, IV = 0 Control group: : I = 0, II = 41, III = 10, IV = 0 | WF10 (n = 50) Control treatment (n = 50) | Response to treatment: Dysuria:WF10 = 24, control group = 22 Frequency: WF10 = 21, control group = 20 Haematuria: WF10 = 36, control group = 31 | Haemoglobinemia (n = 14) |
| Oscarsson et al. (2019) [29] | Hyperbaric oxygen: 12 women, 29 men Control group: 10 women, 28 men | Hyperbaric Oxygen: 64.0 Control group: 64.8 | Hyperbaric Oxygen: EPIC = 48.2 Control group: EPIC = 41.6 | Hyperbaric Oxygen 2.4 atmospheres (n = 40) Control treatment (n = 35) | Full remission: hyperbaric = 29 control group = 12 Partial remission: hyperbaric = 0, control group = 19 | Barotrauma and hyperaemic myopia |
| Mohamadal--Ali et al. (2010) [32] | Hyperbaric oxygen: 3 women, 7 men Control group: 1 woman, 3 men | Hyperbaric oxygen: 79 (59–90) Control group: 63.75 (51–79) | Haematuria without any calibration | Hyperbaric oxygen 2.5 atmospheres (n = 10) Control treatment (n = 4) | Full remission: hyperbaric = 2, control group = 2 Partial remission: hyperbaric = 0, control group = 0 | None |
| Milani et al. (1988) [30] | Flavoxate hydrochloride 600 mg: 21 women Flavoxate hydrochloride 1200 mg: 13 women | Flavoxate hydrochloride 600 mg: 57.28 ±13 Flavoxate hydrochloride 1200 mg: 52.76 ±10.1 | Urgency and incontinence (ICS) Flavoxate hydrochloride 600 mg: 5.52 ±1.53 Flavoxate hydrochloride 1200 mg: 5.15 ±1.77 | Flavoxate hydrochloride 600 mg (n = 21) Flavoxate hydrochloride 1200 mg (n = 13) | Clinical remission of symptomatology: flavoxate hydrochloride 600 mg = 9 Flavoxate hydrochloride 1200 mg = 8 | Mild nausea (n = 3), retrosternal pain (n = 2) |
| Lojanapiwat et al. (2002) [31] | Intravesical formalin: 11 women Gauzes with formalin: 8 women | Intravesical formalin: 50 (44-64) Gauzes with formalin: 58 (54-71) | Haematuria without any calibration | Intravesical formalin injections 4% (n = 11) Placement of 10% formalin impregnated gasses (n = 8) | Full remission: group I = 9, Group II = 6 Partial remission: group I = 0 Group II = 0 | Group I: anuria and bilateral hydronephrosis (n = 2), vesicovaginal fistula (n = 1), death due to sepsis (n = 1) Group II: none |

Hyperbaric oxygen therapy is a reappearing therapeutic aspect that is used in chronic radiation cystitis as well as the other uses in persistent external trauma, especially after radiation. Due to its neoangiogenic and stem cell stimulation properties, it achieves complete resolution of haematuria in almost two-thirds of the patients [36, 37]. In a study conducted by Moses et al. [38], a population of 470 patients were evaluated before and after the use of hyperbaric oxygen therapy. Around 80%

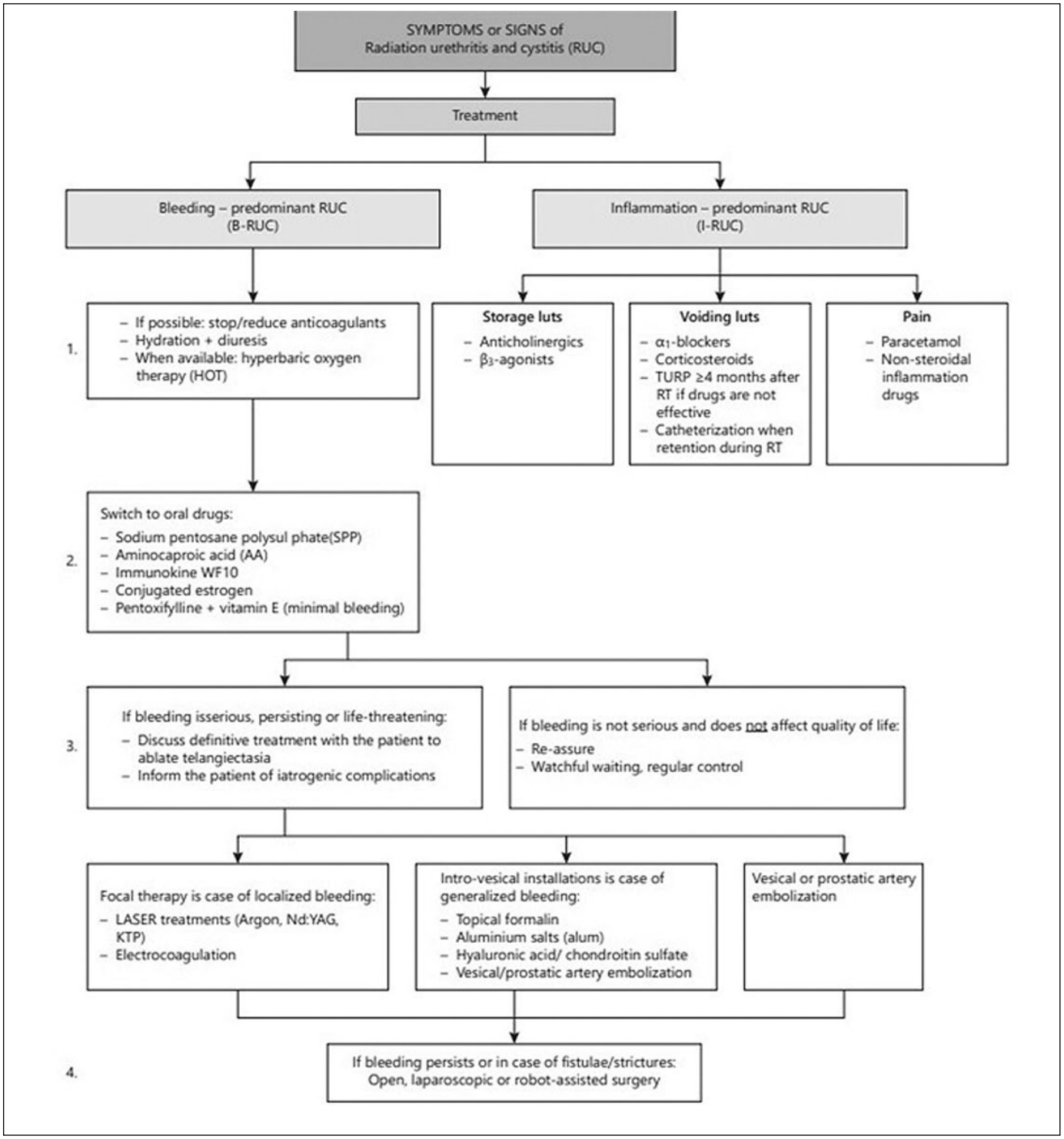


**Figure 6.** *Algorithm for management of chronic post-radiation cystis based on patient symptomatology, according to Vanneste et al. [33].*

of them had complete regression of haematuria (from 2 [IQR 2] to 0 [IQR 2]; $p < 0.001$). A subgroup analysis of the results showed that a history of smoking and a non-prostate cancer history are negative prognostic factors for improvement odds of hyperbaric oxygen therapy (OR = 0.44, 95% CI: 0.21–0.92; $p = 0.03$), (OR = 0.32, 95% CI: 0.10–0.99; $p = 0.05$).
An additional therapeutic approach includes the use of amniotic membrane extract as a novel therapy for chronic radiation cystitis. The rationale behind this therapy is the pro-regenerative properties for the radiated bladder tissue. As is described by the study of Radoit et al. [39], the use of amniotic bladder therapy presents potential benefit based on the improvement of the scores used in accordance with SF-12 Health Survey and other assessment tools and scores. The same results are supported by the study of Lutchka et al. [40], which shows an improvement in the symptomatology of lower urinary tract as early as 2 weeks and maintained for up to 36 weeks for 80% of the population studied. Despite this, some of them can show symptom rebound at 24 weeks.
A future therapy currently under the microscope is the use of mesenchymal stem cells to counter the radiation toxicity effects. This is achieved by preventing fibrosis, inflammation, and vascular damage, which are the hallmarks of radiation-induced cystitis. However, due to its preclinical state, more research is required to establish suitable therapeutic doses, optimal therapeutic routes, and better understanding of their mechanism of action [41].
This study had several limitations. The basic limitations include the design of the included papers and mainly the absence of a common way of reporting symptoms of chronic post-radiation cystitis (reporting via the LENT-SOMA, CTCAE, and EPIC scales or directly quoting the outcome of haematuria by classifying it as complete, partial, or no remission). There is a lack of randomised clinical trials on this topic, resulting in a reliance on non-randomised studies to draw conclusions, which limits the quality of the results.

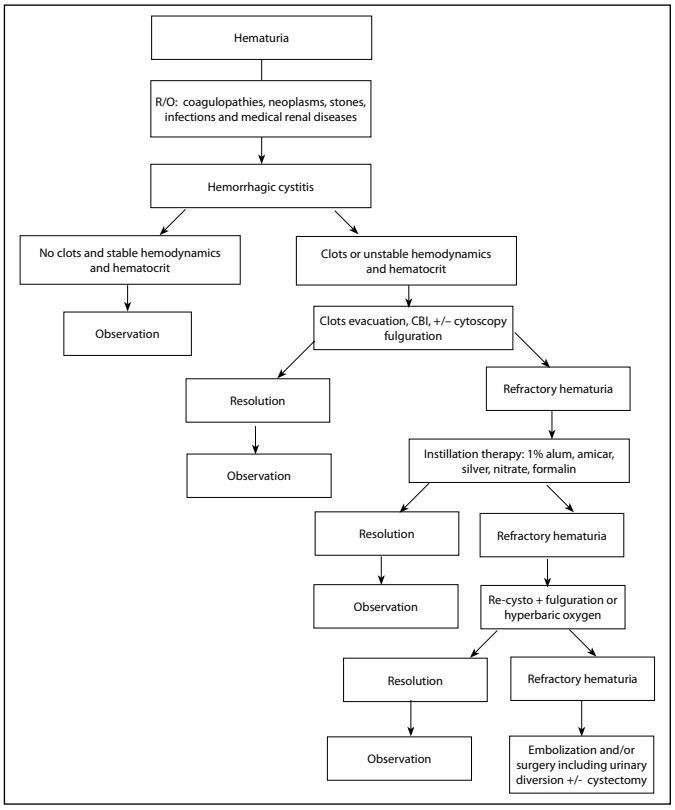


**Figure 7.** *Algorithm for treatment of haematuria, according to Alesawi et al. [40].*

## CONCLUSIONS

Our systematic review was not able to provide an algorithm on how to best manage post-radiation cystitis, despite the multitude of conservative, mainly pharmaceutical, options for the treatment of this condition.
However, a proposed first line of treatment includes administration of antibiotics, analgesics, and epsilon-aminocaproic acid, as well as other haemostatic agents. If there is no remission of symptoms, second-line treatment includes intravesical instillations of aluminium salts, silver nitrate, formalin, or hyaluronic acid solutions, with acceptable success rates. Patients with refractory haematuria are managed with endoscopic cauterisation of the mucosa and clot evacuation. In cases where haematuria persists, patients are managed with selective embolisation of the internal iliac arteries or treated with 100% hyperbaric oxygen.
More randomised clinical trials and/or non-randomised studies with a control arm are required to find the method with the best results in chronic post-radiation cystitis, both in the immediate remission of symptoms, which include not only haematuria but also dysuria (pain in urination, frequent urination), and in the longer duration of symptom-free patients.

### CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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### ETHICS APPROVAL STATEMENT

The ethical approval was not required.

## Appendix

1. Algorithm for searching papers from databases:

### Radiotherapy

#1 exp Radiotherapy/
#2 Radiotherapy/ or "radiotherapy".mp.
#3 exp Radiation injuries/
#4 "rt".fs.
#5 radiat$.mp. (mp=title, abstract, registry number word, mesh subject heading)
#6 radiotherap$.mp. (mp=title, abstract, registry number word, mesh subject heading)
#7 (radio$ adj1 therap$).mp. (mp=title, abstract, registry number word, mesh subject heading)

### Urinary system symptomatology

#8 exp Urination disorders/
#9 (urin$ adj3 frequency).mp. (mp=title, abstract, registry number word, mesh subject heading)
#10 (urin$ adj3 urgency).mp. (mp=title, abstract, registry number word, mesh subject heading)
#11 ((bladder or vesic$) adj3 fibro$).mp. (mp=title, abstract, registry number word, mesh subject heading)
#12 exp Hematuria/
#13 haematur$.mp. (mp=title, abstract, registry number word, mesh subject heading)
#14 hematur$.mp. (mp=title, abstract, registry number word, mesh subject heading)
#15 exp Fistula/
#16 ((bladder or vesic$) adj3 fistul$).mp. (mp=title, abstract, registry number word, mesh subject heading)
#17 ((bladder or vesic$) adj3 ulcer$).mp. (mp=title, abstract, registry number word, mesh subject heading)
#18 exp Urethritis/
#19 urethrit$.mp. (mp=title, abstract, registry number word, mesh subject heading)
#20 exp Urethral stricture/
#21 ((bladder or vesic$ or uret$) adj3 strict$).mp. (mp=title,
abstract, registry number word, mesh subject heading)
#22 exp Hydronephrosis/
#23 hydronephro$.mp. (mp=title, abstract, registry number word, mesh subject heading)
#24 exp Urinary incontinence/
#25 (urin$ adj3 incont$).mp. (mp=title, abstract, registry number word, mesh subject heading)
#26 exp Cystitis/
#27 cystitis.mp. (mp=title, abstract, registry number word, mesh subject heading)
#28 exp Bladder neck obstruction/
#29 (bladder neck adj5 obstruct$).mp. (mp=title, abstract, registry number word, mesh subject heading)
#30 exp Telangiectasis/
#31 telangiect$.mp. (mp=title, abstract, registry number word, mesh subject heading)
#32 Ureteral obstruction/
#33 ((bladder or vesic$) adj5 obstruct$).mp. (mp=title, abstract,
registry number word, mesh subject heading)
#34 (uret$ adj5 obstruct$).mp. (mp=title, abstract, registry number word, mesh subject heading)

### Final Composition

#35 #1 or #2 or #3 or #4 or #5 or #6 or #7
#36 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
or #28 or #29 or #30 or #31 or #32 or #33 or #34
#37 #35 and #36

## References

1. Morris KA, Haboubi NY. Pelvic radiation therapy: Between delight and disaster. World J Gastrointest Surg. 2015; 7: 279-288.
2. Zwaans BMM, Lamb LE, Bartolone S, Nicolai HE, Chancellor MB, Klaudia S-W. Cancer survivorship issues with radiation and hemorrhagic cystitis in gynecological malignancies. Int Urol Nephrol. 2018; 50: 1745–1751.
3. Crew JP, Jephcott CR, Reynard JM. Radiation-induced haemorrhagic cystitis. Eur Urol. 2001; 1 40: 111-123.
4. Sandhu SS, Goldstraw M, Woodhouse CR. The management of haemorrhagic cystitis with sodium pentosan polysulphate. BJU Int. 2004; 94: 845-847.
5. Parsons CL. Successful management of radiation cystitis with sodium pentosanpolysulfate. J Urol. 1986; 136: 813-814.
6. Sommariva ML, Lazzeri M, Abrate A, Guazzoni G, Sandri S, Montorsi F. Intravesical Hyaluronic Acid and Chondroitin Sulphate Improve Symptoms and Quality of Life in Patients with Late Radiation Tissue Cystitis: An Investigative Pilot Study. Eur J Inflamm. 2014; 177-185.
7. Villeirs L, Tailly T, Ost P, et al. Hyperbaric oxygen therapy for radiation cystitis after pelvic radiotherapy: Systematic review of the recent literature. Int J Urol. 2020; 27: 98-107.
8. Ostroff EB, Chenault OW Jr. Alum irrigation for the control of massive bladder hemorrhage. J Urol. 1982; 128: 929-930.

9. Kouriefs C, Gordon S. The management of intractable haematuria. BJU Int. 2001; 88: 301-301.

10. Kavoussi L, Gelstein L, Andriole G. Encephalopathy and an Elevated Serum Aluminum Level in a Patient Receiving Intravesical Alum Irrigation for Severe Urinary Hemorrhage. J Urol. 1986; 136: 666-667.

11. Abt D, Bywater M, Engeler DS, Schmid HP. Therapeutic options for intractable hematuria in advanced bladder cancer. Int J Urol. 2013; 20: 651-660.

12. Westerman ME, Boorjian SA, Linder BJ. Safety and efficacy of intravesical alum for intractable hemorrhagic cystitis: A contemporary evaluation. Int Braz J Urol. 2016; 42: 1144-1149.

13. Brown R. A method of management of inoperable carcinoma of the bladder. Med J Aust. 1969; 1: 23-24.

14. Shah B, Albert D. Intravesical Instillation of Formalin for the Management of Intractable Hematuria. J Urol. 1973; 110: 519-520.

15. Choong S, Walkden M, Kirby R. The management of intractable haematuria. BJU Int. 2001; 86: 951-959.

16. Donahue L, Frank I. Intravesical Formalin for Hemorrhagic Cystitis: Analysis of Therapy. J Urol. 1989; 141: 809-812.

17. Godec CJ, Gleich P. Intractable hematuria and formalin. J Urol. 1983; 130: 688-691.

18. Fall M, Pettersson S. Ureteral Complications after Intravesical Formalin Instillation. J Urol. 1979; 122: 160-162.

19. Amin M, Glynn F, Phelan S, Sheahan P, Crotty P, McShane D. Silver nitrate cauterisation, does concentration matter? Clin Otolaryngol. 2007; 32: 197-199.

20. Goldstein A, D'Escrivan J, Allen S. Haemorrhagic radiation cystitis. British J Urol. 1968; 40: 475-478.

21. Raghavaiah NV, Soloway MS. Anuria following silver nitrate irrigation for intractable bladder hemorrhage. J Urol. 1977; 118: 681-682.

22. Montgomery BD, Boorjian SA, Ziegelmann MJ, Joyce DD, Linder BJ. Intravesical silver nitrate for refractory hemorrhagic cystitis. Turk J Urol. 2016; 42: 197-201.

23. Smit SG, Heyns CF. Management of radiation cystitis. Nat Rev Urol. 2010; 7: 206-214.

24. McGrath M, Benike C, Kuehne F, Engleman E. Effect of WF10 (TCDO) on antigen presentation. Transplant Proc. 1998; 30: 4200-4204.

25. McGrath MS, Kahn JO, Herndier BG. Development of WF10, a novel macrophage-regulating agent. Curr Opin Investig Drugs 2002; 3: 365-73.

26. Srisupundit S, Kraiphibul P, Sangruchi S, Linasmita V, Chingskol K, Veerasarn V. The efficacy of chemically-stabilized chlorite-matrix (TCDO) in the management of late postradiation cystitis. J Med Assoc Thai. 1999; 82: 798-802.

27. Shao Y, Lu GL, Shen ZJ. Comparison of intravesical hyaluronic acid instillation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis. BJU Int. 2012; 109: 691-694.

28. Veerasarn V, Khorprasert C, Lorvidhaya V, et al. Reduced recurrence of late hemorrhagic radiation cystitis by WF10 therapy in cervical cancer patients: a multicenter, randomized, two-arm, open-label trial. Radiother Oncol. 2004; 73: 179-185.

29. Oscarsson N, Müller B, Rosén A, et al. Radiation-induced cystitis treated with hyperbaric oxygen therapy (RICH-ART): a randomised, controlled, phase 2-3 trial. Lancet Oncol. 2019; 20: 1602-1614.

30. Milani R, Scalambrino S, Carrera S, Pezzoli P, Ruffmann R. Flavoxate hydrochloride for urinary urgency after pelvic radiotherapy: comparison of 600 mg versus 1200 mg daily dosages. J Int Med Res 1988; 16: 71-4.

31. Lojanapiwat B, Sripralakrit S, Soonthornphan S, Wudhikarn S. Intravesicle formalin instillation with a modified technique for controlling haemorrhage secondary to radiation cystitis. Asian J Surg. 2002; 25: 232-235.

32. Mohamad Al-Ali B, Trummer H, Shamloul R, Zigeuner R, Pummer K. Is treatment of hemorrhagic radiation cystitis with hyperbaric oxygen effective? Urol Int. 2010; 84: 467-470.

33. Vanneste BGL, Van Limbergen EJ, Marcelissen TA, et al. Development of a Management Algorithm for Acute and Chronic Radiation Urethritis and Cystitis. Urol Int. 2022; 106: 63-74.

34. Alesawi AM, El-Hakim A, Zorn KC, Saad F. Radiation-induced hemorrhagic cystitis. Curr Opin Support Palliat Care. 2014; 8: 235-240.

35. Ju Z, Yu W, Li Y, et al. The clinical research of 5 steps sequential method for whole treatment of hemorrhagic radiation cystitis in China. Int J Med Sci. 2021; 18: 756-762.

36. Pereira D, Ferreira C, Catarino R, et al. Hyperbaric oxygen for radiation-induced cystitis: A long-term follow-up. Actas Urol Esp (Engl Ed). 2020; 44: 561-567.

37. Vanoli S, Grobet-Jeandin E, Mcadam--Gampert S, Louge P, Iselin C, Benamran D. Oxygénothérapie hyperbare dans le traitement de la cystite radio-induite [Hyperbaric oxygen therapy for the treatment of radiation-induced cystitis]. Rev Med Suisse. 2022; 18: 2274-2277.

38. Moses RA, Hunter AE, Brandes ER, et al. Patient-Reported Outcome Measures Following Hyperbaric Oxygen Therapy for Radiation Cystitis: Early Results From the Multicenter Registry for Hyperbaric Oxygen Therapy. J Urol. 2024; 211: 765-774.

39. Radoiu C, Jeberaeel J, Madan R, et al. A preliminary report assessing the feasibility and effectiveness of amniotic bladder therapy in patients with chronic radiation cystitis. Can J Urol. 2023; 30: 11607-11612.

40. Lutchka J, Vercnocke J, Fisher E, et al. Treatment of chronic post-radiation cystitis with trans-urethral amniotic bladder therapy appears durable at 9 months: A clinical study. Urologia. 2024; 91: 623-627.

41. Helissey C, Cavallero S, Guitard N, Théry H, Chargari C, François S. Revolutionizing Radiotoxicity Management with Mesenchymal Stem Cells and Their Derivatives: A Focus on Radiation-Induced Cystitis. Int J Mol Sci. 2023; 24: 9068.